

# CLINICAL CONFERENCE

## The Treatment of Subacute Bacterial Endocarditis

UNIVERSITY OF CALIFORNIA HOSPITAL STAFF CONFERENCE, OCTOBER 2, 1946

**C**ASE presentation, \*Dr. Herbert Moffitt, Jr.: A 65-year-old white machinist was admitted on June 20, 1946. Since May, 1945, patient had had intermittent episodes of chills, fever, sweating, malaise, and anoroxia associated with anemia and thirty pound weight loss. He has been hospitalized elsewhere on eight occasions and treated with penicillin and transfusions with resultant relief of symptoms for two or three weeks. In March, 1946, blood culture was reported positive for streptococcus viridans for the first time. In April, 1946, he had an episode of acute pulmonary edema. There had been no evident embolic phenomena. There was no history of rheumatic fever although a murmur had been noted twelve years before entry when he was granted an insurance policy.

Examination at entry on June 20, 1946, revealed the following positive findings: (1) Erythematous macular rash over trunk and arms; (2) Petechial hemorrhages on right hand (three) and left foot (two). (3) Loud, harsh, widely-transmitted apical systolic murmur without thrill or cardiac enlargement. (4) Splenomegaly two finger-breadths below costal margin. (5) A rectal polyp 10 cm. above the sphincter.

Significant laboratory findings at time of admission included: Hgb.: 92 per cent, RBC: 4.04 million, WBC: 7,600 with normal differential, CSR: 36 mm./hr. Urino gravity 1.023; albumin 3 plus; 5 WBC and 5 RBC per HPF; hyaline and granular casts. Chest x-ray and EKG were consistent with left auricular enlargement. Circulation time, venous pressure, and vital capacity were normal. Biopsy showed the rectal polyp to be a malignant pailoma; it was excised and the base was cauterized.

During the first week of hospitalization, fever spiked to 40.7 with chills; five blood cultures were positive for streptococcus viridans: the organism was sensitive to 0.01 units penicillin per cc. During the second week the patient was given 400,000-500,000 units of penicillin daily by continuous intramuscular drip with a resultant blood level of 0.31 units/cc. Dosage was increased to 1,500,000 units daily during the last week of July and continued in this dosage in spite of low grade fever and occasional spikes to 38.6 until August 26, when continuous penicillin was discontinued, after a total dosage of 68,300,000 units. On September 3, 30cc. of pus was evacuated from an abscess at the site of previous catheterization in the right lateral thigh but this pus was not cultured. During

hospitalization, patient was given three transfusions; he had an episode of acute pulmonary edema following the last transfusion but this cleared in six hours of treatment with oxygen, morphine, and aminophyllin. He had been previously digitalized.

The patient was discharged on September 12, after being afebrile and symptom free 19 days after the cessation of specific therapy. At time of discharge, all blood cultures had been negative for two months, Hgb was 80 per cent, RBC 4.08 million, WBC 7,800, CSR 27 mm./hr. Urine showed 1 plus albumin, few WBC, rare granular cast.

\*Dr. Kerr: I am asking Dr. Rantz to open the discussion and will ask him and the other discussants to bring out the following points:

1. What is the best method of administration of penicillin?
2. What is the validity of the penicillin blood level and the sensitivity of the organism as indices of penicillin dosage? How much can we rely on sensitivity and blood levels so as not to waste the drug?
3. What is the proper dosage and how often, how much and how long?
4. What are the criteria for cure?

\*\*Dr. Rantz: The manner of administration and the duration of therapy in the group treated here and that at Stanford Hospitals is really quite different. I cannot attempt to answer all of Dr. Kerr's questions this morning. There are many variables in the treatment of this disease. The total duration of the therapy was kept constant in our patients who received therapy for 60 days. If the patient needed more treatment, another course of 60 days was given. We also control the factor of route of administration by using three hour intermittent intramuscular therapy which may, on the whole, be more satisfactory than continuous therapy. There is no way to settle this. With intermittent therapy we have treated patients with smaller daily doses than the California group has been required to use.

We have studied 32 patients at Stanford, 20 of whom received 300,000 units per day for 60 days. In all the strain of streptococcus was inhibited by .05 units per cc. of penicillin; all were bacteriologically cured. In the beginning when patients were first admitted to the clinic it was impossible to increase the daily dose of penicillin. As more

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of the drug became available, we began to use more and more in certain cases. We have several patients who have had more than one course of penicillin. We have estimated the daily dose as 1,000,000 units for each tenth of a unit of sensitivity to the organism. Nine cases have recovered in which more than 1,000,000 units per day were given. One case was of some interest and raises another point of great importance which was not appreciated previously. This is the matter of renal function.

Many blood level determinations have not been done but we have been interested in excretion of penicillin studies carried out in this patient, which demonstrated that he cleared only 125 cc. of blood per minute of penicillin instead of the normal 600 or 700 cc. His blood levels were, therefore, several times higher than would be expected in a normal person. A cure was obtained with a dose of 12,000,000 units per day although his organism required 5.0 units per cc. of penicillin for complete inhibition *in vitro*.

It is possible to predict dosage on the basis of sensitivity with some accuracy, but there is a tendency to use larger amounts of penicillin even though we know that cure may be usually obtained with smaller dosage. We feel that the most reliable sign is a sterile blood culture. No other clinical or laboratory criteria for cure are very helpful. To determine if the disease is arrested, it is necessary to carry out an adequate course of therapy, withdraw the drug, and follow the patient clinically and with blood cultures.

†Dr. Brown: Subacute bacterial endocarditis is a complicated disease. We cannot approach it as a simple infection for which we can plan routine methods of treatment. Heart damage is always present and is even more extensive after treatment when the infecting organisms have been eliminated and the valves have healed. Many patients will develop congestive failure from which they will succumb. In spite of present methods of therapy the disease remains extremely serious and we should approach the problem with humility. Up to about a year ago recovery rates were estimated at little better than 40 per cent. Now more patients are being cured of the infection. Theoretically all patients with subacute bacterial endocarditis due to penicillin sensitive organisms should be cured of the infection. Heart damage then remains. However, many recovered patients live useful lives and the ultimate prognosis of any patient is difficult to predict so that all should be regarded with optimism.

Since treatment is antibacterial in nature, the infecting organism and its sensitivity to penicillin is of first importance and must be determined at the outset. The alpha hemolytic streptococcus (*streptococcus viridans*) is the cause in the vast majority of patients. Fortunately most strains are

relatively sensitive to penicillin. Strains of *streptococcus faecalis* are perhaps next most frequent. These are in general less sensitive and must be differentiated from *strept. viridans*. Almost all pathogenic organisms are capable of causing subacute bacterial endocarditis in rare instances. It is obviously of the greatest importance for treatment and an evaluation of prognosis to promptly determine the nature and characteristics of the infecting organism in any case.

A consideration of the best method of administration of penicillin raises differences of opinion. We have preferred the continuous intramuscular injection method for several reasons. It seemed easier on the patient to have a soft catheter continuously in the muscle with an infusion bottle attached than to receive repeated injections over many weeks. Most patients agree. It also seemed more convenient for the ward staff. Finally it has been our opinion that the maintenance of a continuous effective blood level was more rational than to obtain intermittent peaks; this last is controversial as mentioned before. Other methods of administration such as the oral, intravenous, etc., have drawbacks which make them less desirable than the intramuscular route.

The criteria for cure of subacute bacterial endocarditis are difficult to determine. Obviously if the blood culture remains positive the infection is still active. However, if the blood culture is negative, infection on the heart valve may still be present and become active when penicillin is stopped. Fever, embolic phenomena and elevated sedimentation rate may continue for a short time even though recovery has taken place and are therefore not reliable as guides to continuing infection. We hope to develop tests which will indicate when infection has been eliminated. Since patients with subacute bacterial endocarditis have significant amounts of antibody in their blood against the infecting organism and normal people do not, measurement of this level might be a guide. Supposedly, after cure these antibodies will disappear. We have employed precipitin tests to measure antibodies against the alpha hemolytic streptococcus. To date all patients have had antibodies but they have remained during treatment. These immune bodies will probably not disappear for several weeks and so such measurements can constitute only a late guide to cure.

\*Dr. Friedlander: Two of four patients recently seen developed subacute bacterial endocarditis following dental extractions. We should be able to give penicillin in adequate prophylactic dosage to patients who have heart disease and who must undergo oral surgery.

Dr. Kerr: This prophylactic measure might be used in other types of surgery, also. Some patients have been treated for long periods of time. Observations have been made which indicate that

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when one uses an antibiotic like penicillin which eliminates certain organisms, other organisms may grow. It has been suggested that large doses

of penicillin given by mouth may cause the development of such a condition as the brown tongue associated with monilia.

### PENICILLIN SPRAY ECONOMIC WAY TO TREAT RESPIRATORY DISEASES

Inhaling penicillin spray is more economical and effective for infections of the respiratory tract than injecting of the respiratory tract than injecting the drug into the veins or muscles, according to the latest report appearing in the October 5 issue of *The Journal of the American Medical Association*.

Frank W. Morse, M.D., of Lawrencetown, Nova Scotia, says that by this treatment penicillin is placed at the site of infection and has not only a strong local effect but it is absorbed into the blood stream and aids the natural body defenses to overcome the condition. Moreover, "it also has a definite local soothing effect which relieves such discomfort as soreness in the throat, painful, frequent coughing and the sensation of dryness in the mucous membranes."

The author maintains that the "penicillin seems to act in a more efficient manner when given by spray than by injection. It is common to give 160,000 units daily by the intramuscular route in pneumonia, whereas in treatment of one case of pneumonia in this series 40,000 units was given daily for four days, a total dosage of 160,000 units in all. In other words, the total dose in this case treated by spray would supply only one day's dose if given intramuscularly. This saving of penicillin is apparently due to the fact, that, first, the greatest concentration of penicillin is directly on the infected site, the air sacs, and secondly, it is absorbed into the blood stream and thus has a systemic effect as well."

Most of the 25 patients who were treated by this physician were infected during the influenza epidemic which began in this locality about January 3, 1946. There were only two failures in this series, due to the uncooperativeness of the patients.

Penicillin spray is produced by a hand-operated bulb atomizer. The patient inhales and then holds his breath, allowing the suspended penicillin to settle on the infected mucous membranes.

Personally convinced of the advantages of penicillin spray, the author summarizes them as follows:

1. The absence of toxicity in contrast to that of the sulfonamides.

2. The absence of dangers due to untrained personnel using the intramuscular route of administration.

3. The ease of transporting and caring for the materials, the atomizer and penicillin.

4. The availability of materials. Atomizers can be easily obtained and are cheap. Penicillin spray can be purchased at a small cost.

5. Painless administration. This is an important factor in nervous or young patients.

6. The saving of penicillin.

7. The remarkably soothing local effect of penicillin spray in addition to its therapeutic effectiveness.

8. The pleasant taste of penicillin.

9. The absorption of inhaled penicillin. The fact that inhaled penicillin spray is absorbed and can attain an effective level in the blood suggests that perhaps sites of infection other than those in the respiratory tract may be treated in this manner.

An editorial in the same issue of *The Journal* states that penicillin spray is probably the simplest technique thus far employed for the treatment of respiratory conditions. "The results recorded are encouraging," it says, adding: "However, much more needs to be done on the subject of penicillin administration by inhalation before this procedure can be considered of established scientific merit. Controlled studies are necessary. Large enough numbers of patients with a single respiratory disease need to be studied and compared with similar groups treated without penicillin and with penicillin administered by the usual intramuscular route. Comparative studies should be made on the value and accuracy of the various types of nebulizers and on their effectiveness in delivering the penicillin where it will do the most good. Important also are careful studies on the optimum dosage of penicillin when given by spray, the preferred frequency of administration and the most desirable medium for dissolving the penicillin."

